Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 37, No. 2, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(00)01155-4

Lack of Efficacy of Atenolol for the Prevention of Neurally Mediated Syncope in a Highly Symptomatic Population: A Prospective, Double-Blind, Randomized and Placebo-Controlled Study

Antonio H. Madrid, MD, Javier Ortega, MD, Jose G. Rebollo, MD, Juan G. Manzano, MD, Javier G. Segovia, MD, Andrés Sánchez, MD, Gonzalo Peña, MD, Concepción Moro, MD

Madrid, Spain

OBJECTIVES This study was designed to evaluate the efficacy of atenolol for the long-term management of patients with vasovagal syncope. The primary hypothesis was that atenolol is not superior to placebo for the treatment of vasovagal syncope.

BACKGROUND There is no definitive well-controlled analysis of the efficacy of beta-adrenergic blocking agents in patients with recurrent vasovagal syncope.

METHODS This is a prospective, randomized, double-blind, placebo-controlled study. Fifty patients with recurrent vasovagal syncope were included (at least two episodes in the last year). A baseline tilt test was performed. Twenty patients (40%) had a positive tilt test. Intravenous atenolol prevented a second positive tilt in five patients. The patients were randomized to receive either atenolol or a placebo (26 patients atenolol 50 mg/day, 24 patients placebo). The follow-up procedure lasted one year. The primary end point of the study was the time to first recurrence of syncope.

RESULTS In the intention-to-treat analysis, the group treated with atenolol had a similar number of patients with recurrent syncopal episodes as the placebo group. The Kaplan-Meier actuarial estimates of time to first syncopal recurrence showed that the probability of remaining free of syncope drops similarly in both groups and that there was no statistical difference between both curves (patients treated with atenolol vs. the placebo) with a log-rank test p value of 0.4517.

CONCLUSIONS The recurrence of neurocardiogenic syncope in highly symptomatic patients treated with atenolol is similar to that of patients treated with placebo. (J Am Coll Cardiol 2001;37: 554–9) © 2001 by the American College of Cardiology

The optimal approach to the treatment of patients with neurocardiogenic syncope remains uncertain (1,2). Many types of treatment have been proposed that are based largely on small nonrandomized studies and clinical series. There is a remarkable absence of data from randomized and prospective clinical trials (3–14). The triggering event for an episode of vasovagal syncope is thought to be an increase in

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adrenergic tone resulting in the activation of cardiac mechanoreceptors. Beta-adrenergic blocking agents would act by inhibiting the activation of the left ventricular mechanoreceptors because of their beta-blocking, blocking the initial increase in adrenergic tone and negative inotropic effects. There are, however, few well-controlled analyses on the efficacy of beta-blockers (15–21). Thus, we began this study in an attempt to establish the efficacy of atenolol in the treatment of vasovagal syncope.

From the Arrhythmia Unit, Cardiology Department, Ramón y Cajal Hospital, Alcalá University, Department of Medicine, Madrid, Spain. Supported, in part, by a grant from AstraZeneca, Spain.

Manuscript received November 16, 1999; revised manuscript received September 5, 2000, accepted October 26, 2000.

METHODS

Patients. We included 50 patients in this study. They were recruited consecutively from patients referred to our arrhythmia unit. All the patients had a clinical history consistent with the diagnosis of recurrent vasovagal syncope. Substantiation of the diagnosis was based on their clinical histories: a transient loss of consciousness with the typical precipitating factors (triggers: prolonged standing, pain, the sight of blood, a warm environment or hot shower and stressful situations) and prodromal symptoms (palpitations, severe light-headedness associated with nausea and diaphoresis). The inclusion criteria were: age 18 to 75 years with at least two syncopal events during the previous year. A complete study (physical examination, 24-h ambulatory electrocardiogram, echocardiography, bilateral carotid sinus massage, routine hematological and biochemical investigations, 12-lead surface electrocardiogram and chest X-ray) was performed to eliminate other possible causes of syncope in all patients during the inclusion phase. Potential arrhythmic causes of these syncopal episodes were excluded based on the absence of structural heart disease and arrhythmic events during 24-h Holter monitoring or clinical data that could suggest an underlying arrhythmia. Exclusion criteria were: 1) pregnancy or lactation; 2) the presence of another

possible etiology for syncope; 3) severe peripheral arterial disease, diabetes mellitus, atrioventricular conduction disturbances (intraventricular conduction defects or an abnormal PR interval) or documented autonomic dysfunction (chronically impaired sympathetic efferent activity so that vasoconstriction is deficient; upon standing, blood pressure always falls, i.e., orthostatic hypotension, defined as a decrease of at least 15 mm Hg); 4) hypersensitivity or any other contraindication for beta-blocker therapy; 5) neoplastic or psychiatric diseases; 6) drug addiction or any other medical condition that, in the opinion of the investigators, could make the patient inappropriate for the study.

Clinical data. The mean age of the patients was 31 ± 10 years; 30 were female, and 20 were men. The mean duration of symptoms was 65 ± 57 months. The median number of syncopal events per patient during the year before the inclusion in the study was three. All the patients had a blood pressure and heart rate within normal limits: systolic mean blood pressure: 121 ± 3 mm Hg, diastolic: 71 ± 2 mm Hg, mean heart rate 67 ± 2 beats/min. The results of the tests performed during the inclusion phase were normal in all patients.

Study design and end points. This is a prospective, randomized, double-blind and placebo-controlled study on the efficacy of atenolol versus placebo for the treatment of recurrent vasovagal syncope in a general population with a high number of syncopal episodes. The primary hypothesis was that atenolol is not superior to a placebo for the treatment of vasovagal syncope. The study protocol was approved by the ethics committee of the hospital. Written informed consent was obtained from each patient.

During the first visit all patients underwent a tilt-table test. In the patients with a positive response, a second tilt test with intravenous atenolol was performed. The patients were then randomized to receive oral atenolol (50-mg pills) or a placebo—one pill every day (regardless of the result of the tilt test). The pills were identical in shape, color and size. The patients were then followed up for one year. Examinations were performed every two months. At each examination, an accurate history, a physical examination and an electrocardiogram were performed. The clinical recurrences of the syncope and possible adverse effects were evaluated. In the case of recurrences, the drug could be increased to 100 mg daily if tolerated. In the case of adverse effects or intolerance, the dose could be decreased to 25 mg daily. The boxes were returned after each visit. Drug compliance was assessed by pill counting.

Criteria for withdrawal from the study included the patient's refusal to continue, noncompliance, protocol violation or serious adverse events. Patients who dropped out because of intolerable adverse effects of the drug or because they had no therapeutic response with severe symptoms were considered completed cases for the intention-to-treat analysis. The code was not broken until the end of the study.

The main objective of this study was to evaluate the efficacy of oral atenolol to prevent recurrences of vasovagal syncope in a highly symptomatic population. The primary end point of the study was the time to first recurrence of syncope.

Tilt-test protocol and definitions. The patient was placed in a supine position on a motorized tilt table with footboard support. An intravenous catheter was placed in an arm vein for an infusion of 5% glucose solution and the administration of emergency medications, if necessary. Continuous electrocardiographic monitoring was recorded, and noninvasive automated blood pressure monitoring was performed (Finapress digital photoplethysmography: Ohmeda, Madison, Wisconsin). Blood pressure and heart rate were continuously recorded. After a 10-min supine control phase, the patients were tilted upright to an angle of 80° for 45 min or until a positive response was achieved. A positive response was defined as: 1) reproduction of the symptoms that had been associated with the patient's clinical events or 2) a sudden loss of consciousness or the development of presyncope in association with an abrupt decrease in systolic blood pressure of 30 mm Hg or 20% to 30% of previous values. We considered three types of syncope according to the changes in heart rate and blood pressure detected during the episodes: 1) vasodepressor, with an abrupt decrease of systolic blood pressure over 30 mm Hg (or 20% to 30% of the basal value); 2) cardioinhibitory, with a decrease in heart rate over 20% of the measurement taken immediately before the episode and 3) a mixed response, with both bradycardia and hypotension.

If a positive response occurred during the upright tilt, patients were returned to the supine position, and the test was terminated. All the patients with a positive test underwent an infusion of intravenous atenolol (3 h after the first tilt test). The dose of atenolol varied from 5 to 10 mg depending on a heart rate higher than 50 beats/min and blood pressure, with a decrement <25% over baseline. A second tilt test was then performed following the same protocol.

Sample size calculation. The sample size calculation was based on an estimated efficacy of 70% for atenolol and 25% for the placebo, with an alpha level of 0.05 and a test power of 0.80. The resulting sample size was 23 patients for each treatment group. Most of the published reviews of the treatment of vasovagal syncope advise the use of beta-blockers for the treatment of vasovagal syncope. Moreover, it is well known that these patients could improve even without any specific treatment, after counseling. We took these percentages as an estimation from the published data (22,23).

Statistical analysis. The primary analysis of the results of the study was by intention-to-treat analysis. The time to first syncopal recurrence was analyzed using the Kaplan-Meier curves and compared using the log-rank test. Hazard ratio and its confidence intervals were estimated using the Cox regression model. The statistical package used was SPSS 9.0 for Windows. Means (± standard deviation) and medians were calculated for continuous variables, and fre-

Table 1. Baseline Clinical Data of Patients

	Atenolol n = 26 Patients	Placebo n = 24 Patients	p Value
Mean (±SD) age, yrs	32 ± 12	31 ± 8	0.37
Men/women	11/15	9/15	0.50
Mean duration of symptoms before the study (months)	68 ± 50	61 ± 64	0.37
Median number of syncopes per patient	3	3	0.215
Supine systolic arterial blood pressure, mm Hg	118 ± 12	120 ± 12	0.34
Supine diastolic arterial blood pressure, mm Hg	70 ± 7	73 ± 6	0.13
Heart rate, beats/min	68 ± 5	70 ± 8	0.19

quencies were measured for categorical variables. Differences between groups were examined for statistical significance by a Student *t* test for continuous variables, with the Mann-Whitney *U* test for the variables nonparametrically distributed and by Fisher exact test for categorical variables. A p value <0.05 was considered significant.

RESULTS

About 700 patients with unexplained syncope were referred to us for evaluation in our arrhythmia unit. About 300 of these (43%) had a clinical history consistent with vasovagal syncope. Two hundred thirty patients were ineligible for the study due to: only one syncopal episode during the previous year (148 patients), age < 18 years (53 patients), age > 75 years (12 patients), diabetes mellitus (14 patients), organic heart disease (36 patients), abnormal electrocardiogram (27 patients), possible pregnancy (6 patients), psychiatric disease (4 patients) and another 18 patients who had more than one reason. Seventy patients met the inclusion criteria. Of these, 50 gave their informed consent to take part in the study; 26 were randomly assigned to the atenolol arm and 24 to the placebo arm. The patients were followed up for one year, independently of the recurrence of syncopal episodes. Forty patients completed the protocol of the study, and 10 patients discontinued the study. The compliance of the patients that remained in the study was 100%.

Clinical data. The clinical characteristics of the patients included in the study are summarized in Table 1. The median number of syncopal events per patient during the year prior to the inclusion in the study was three in patients treated with atenolol, with no difference in comparison with patients treated with placebo, who also had a median number of syncopal events of three.

Head-up tilt test. With the tilt test, twenty patients (40%) showed a positive response, whereas 30 showed no change during the tilt test. The group with a negative tilt test result was made up of: 30 patients, with a mean age of 35 ± 10 years, 19 female, mean duration of symptoms 65 ± 59 months; 18 of these patients were treated with atenolol and 12 with placebo. The group with a positive result from the initial tilt test was made up of: 20 patients, with a mean age of 27 ± 8 years, 11 female, mean duration of symptoms 65 ± 55 months; 8 were treated with atenolol and 12 with placebo. There were no significant differences between the two groups (patients with a positive versus negative tilt test) with respect to age, gender, blood pressure, heart rate and number of syncopal events. In tilt positive patients, six had a vasodepressor response, five a predominant cardioinhibitory response and nine a mixed response. Eighteen of the 20 patients who had a positive response received intravenous atenolol before a second tilt test was performed. Atenolol prevented a second positive response in only five patients (25%). In patients with a predominant cardioinhibitory response (five patients), atenolol did not prevent a second positive response in any of them.

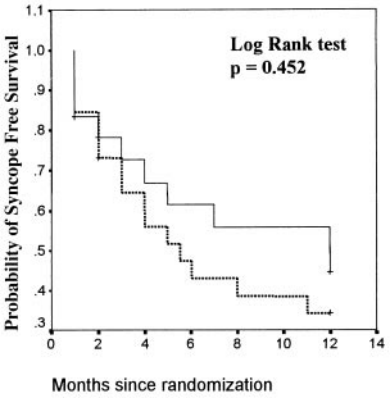

Figure 1. Primary hypothesis of the study. Kaplan-Meier estimates of the probability of remaining free of syncopal recurrence (time to first syncopal recurrence) in the patients treated with atenolol or the placebo. **Dotted line** = atenolol; **solid line** = placebo.

Efficacy during long-term treatment. The median number of syncopal events during the follow-up procedure was two for those patients treated with atenolol and 0 for those patients treated with placebo (p = 0.215). This difference was not statistically significant although it appears that the recurrence rate of syncope drops in both groups, simply after tilt-table testing. In the intention-to-treat analysis, the group treated with atenolol had a similar number of patients with recurrent syncopal events as the placebo group (16 and 11 patients, 61.5% and 45.8%, respectively, in each group, p = 0.09). The median time to the first recurrence of a syncopal event for all the patients was seven months, with a standard error of 3.77 and 95% confidence interval between 0 to 14.39 months. The Kaplan-Meier actuarial estimates of first syncopal recurrence showed that the probability of remaining free of syncopal events drops similarly in both groups. There was no statistical difference between both curves (patients treated with atenolol vs. the placebo), with a p value of 0.4517 (Fig. 1). Atenolol was associated with a 38% increase in the rate of recurrent syncope, relative risk 1.38 (0.64 to 3.01), but there was no difference in these two groups (atenolol or placebo) given that the confidence intervals are extremely wide (p = 0.405).

Data were analyzed depending on the outcome of tilt-table testing. To find out the possible difference in the

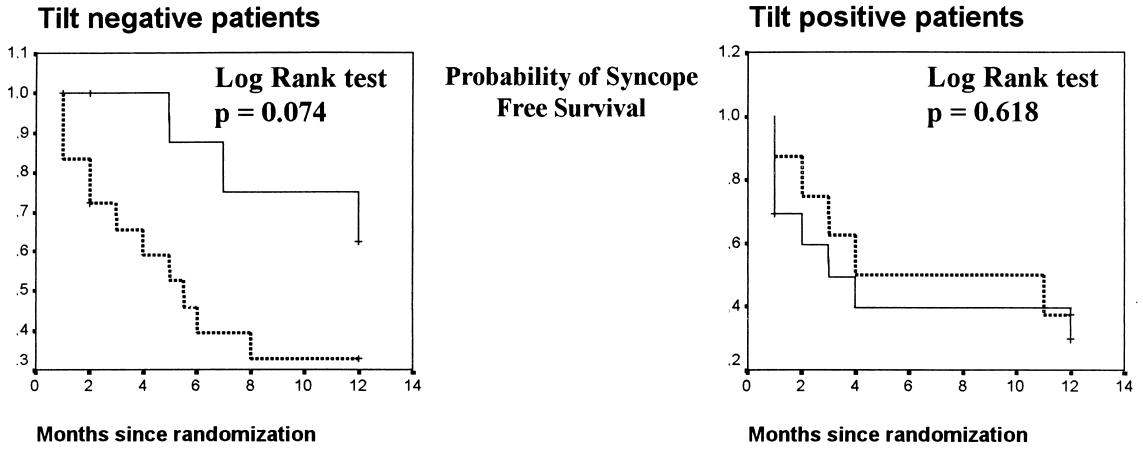

Figure 2. Analyses of the data stratified by the outcome of tilt-table testing. Kaplan-Meier curves for the patients with tilt positive and tilt negative results, time to first syncopal recurrence in the patients treated with atenolol or the placebo. **Dotted line** = atenolol; **solid line** = placebo.

natural history of patients according to the result of the tilt test, we compared the outcome of patients with a positive or negative tilt-table test result in the placebo group. A positive tilt-table test was associated with an increased risk of recurrent syncope: relative risk 3.39 (0.89 to 12.95). However, it did not reach statistical significance ($p = 0.0582$). The probability of syncope-free survival was analyzed using the Kaplan-Meier curves comparing patients with negative tilt test treated with atenolol and patients treated with the placebo. These were not statistically different, $p = 0.0744$, although there seemed to be a trend towards a better outcome for patients treated with placebo. The Kaplan-Meier curves (probability of syncope-free survival) between patients with positive tilt test treated with atenolol and patients with the placebo were not statistically different, $p = 0.6184$ (Fig. 2).

Adverse events. A total of five adverse events were registered: four in patients treated with atenolol and one occurring in the placebo group ($p < 0.05$). Four of them were judged as being possibly related to the treatment. Fatigue, bradycardia and headache were observed in three patients treated with atenolol, and alterations of the libido were observed in one patient treated with placebo. No deaths or serious syncopal event-associated traumas occurred during the study.

DISCUSSION

Therapy of vasovagal syncope. Syncope is one of the most common clinical problems in medical practice. The treatment of patients with vasovagal syncope is still a subject of controversy. This controversy exists for several reasons: 1) the natural history of vasovagal syncope is still not well known, with a clustering behavior and long periods without any symptoms; 2) there is a lack of consensus, and both randomized and controlled studies are needed. Many drugs have been used for this purpose (disopyramide, transdermal scopolamine, fludrocortisone, etilefrine, beta-blockers, etc.) (3–14). None of the drugs has been unequivocally proven for long-term effectiveness, based on adequate randomized controlled clinical trials. The frequency of syncopal events decreases significantly in patients with vasovagal syncope during follow-up procedures after a positive response in a head-up tilt test, even with no specific treatment. However, this could be due both to the role that the tilt test plays in the treatment of these patients and the medical advice. Several studies have demonstrated no significant effect of drugs in preventing vasovagal syncope, such as disopyramide (3), scopolamine (4) and etilefrine (VASIS) (6). Midodrine has been used with better results (8,9). With regard to placebo control, a few trials have demonstrated benefits (8,17,24,25). Pacing may be a therapeutic alternative for some patients with recurrent vasovagal syncope although more randomized controlled studies are needed (10,11,26).

Role of tilt-table testing. There is a general consensus that tilt-table testing is an important diagnostic tool in the evaluation of patients with unexplained syncope, with a good sensitivity (27,28) or specificity (29–32) in the absence of high doses of isoproterenol. The clinical history should continue to be the "gold standard" for the diagnosis of vasovagal syncope, and, for this reason in our study, patients with both positive and negative tilts were followed up. Furthermore, a positive tilt table test may be associated with a higher rate of recurrent syncope, and our data show that a positive tilt (for placebo patients only) was associated with an increased risk of having recurrent syncope, relative risk 3.39 (0.89 to 12.95), $p = 0.058$. The value of the head-up tilt test to qualify drugs for use in vasovagal syncope or for predicting treatment efficacy is less certain. The therapeutic value of serial tilting has been recognized (33). The baroreceptor response may be conditioned by serial tilt-table tests. This remedy can be combined easily with the general recommendations.

Beta-adrenergic receptor blocking drugs. Beta-blockers have been widely used in the treatment of patients with neurocardiogenic syncope, and they are frequently chosen as a first line drug therapy. They were proposed more than a

decade ago for use in preventing recurrent episodes of vasodepressor syncope (34). These agents presumably exert their effects by diminishing the degree of cardiac mechanoreceptor stimulation or by blocking the effects of high levels of circulating catecholamines. Metoprolol, pindolol and atenolol have been the most frequently studied beta-blockers in vasovagal syncope. But, from an evidence-based medicine point of view, the data that support this assertion are dubious. As far as we know, the only randomized, double-blind, placebo-controlled trial to evaluate the efficacy of oral beta-blockers in the treatment of neurocardiogenic syncope is the one performed by Mahanonda et al. (17). They compared the efficacy of a beta-blocker (atenolol) with a placebo in patients who had at least one episode of syncope or two episodes of presyncope one month before presentation. They randomized patients into an atenolol or placebo group. The response rate (negativization of tilt-table test) after one month of treatment was 62% versus 5% ($p = 0.0004$) in the atenolol and control groups, respectively. Patients who received atenolol reported feeling better compared with those who received placebo (71% vs. 29%, $p = 0.02$). The main limitation of the study was the short follow-up period (only one month), bearing in mind that we are dealing with patients with a disease (neurocardiogenic syncope) with an unknown natural history. Patients who have had many syncopal events in one month, for example, may remain asymptomatic for long periods of time. In addition, studies that evaluate drug efficacy in the treatment of such a disease should have a longer follow-up period.

There are other studies that have evaluated the efficacy of beta-blockers. Not all of them are randomized or placebo-controlled studies. Sheldon et al. (15) studied the effects of beta-blockers on the time to first syncope recurrence in a controlled parallel, but not randomized, study. Syncope recurred in 17 of the 52 patients who received beta-blockers and in 28 of the 101 patients who were untreated. They concluded that the treatment with these drugs had no significant effect on preventing syncope recurrence. Cox et al. (16) prospectively evaluated the efficacy of propranolol (both intravenous during head-up tilt testing and oral in the long-term) for preventing neurocardiogenic syncope. Oral beta-blockers were effective by tilt-test criteria in 94% of the patients, and 10% had recurrent clinical symptoms while taking beta-blockers (atenolol, propranolol, metoprolol and nadolol). Their conclusion was that intravenous propranolol was very effective in blocking the abnormal neurocardiogenic reflex during tilt testing and that it could predict a good response to oral beta-blockers. This study was not placebo-controlled, and the type of beta-blocker therapy was not randomized. Natale et al. (12) published a report on the treatment of 303 patients with a history of syncope together with a positive head-up tilt. The recurrence of symptoms was very low in this study, 12 of the 210 patients treated according to the response to repeat head-up tilt, 130 of which were on metoprolol. This study was a retrospective analysis and was neither randomized nor controlled.

In our study, we evaluated the efficacy of a beta-blocker, atenolol, compared with a placebo in preventing recurrences in patients with clinically diagnosed vasovagal syncope. The end point was the time to first recurrence of syncope. Intravenous atenolol was not an efficient drug in preventing a second positive tilt test (only 25% of the patients). The positive response to intravenous atenolol could not even predict a good response to chronic oral administration. The patients included in our study were highly symptomatic and had more syncopal episodes before participating than the patients in some of the other studies, which probably accounts for the high recurrence rate in this study. After one year of follow-up, there were no statistical differences between patients treated with atenolol and patients treated with the placebo. There are several main contributions of our study. As far as we know, this is the first double-blind, randomized, placebo-controlled trial on the efficacy of beta-blockers for the treatment of neurally mediated syncope with a long-term follow-up (one year). The benign course of neurocardiogenic syncope may give the false impression of drug (or pacemaker) efficacy. Randomized controlled studies are essential to the assessment of the real usefulness of any proposed therapy for patients with vasovagal syncope (1,2).

Study limitations. There is not a "gold standard" method for diagnosing vasovagal syncope. This fact will always be difficult in the management of this important and frequent clinical entity. Some of our patients could, in fact, have another diagnosis although is very improbable because of the consistent clinical history and the lack of new diagnosis during the follow-up. In any case, this is a highly symptomatic population, in which we feel that there is a necessity to treat and to find out the results of any implemented treatment. The relatively small number of patients included makes it difficult to arrive at any firm conclusions to many secondary aspects of our study. We did not use the tilt test to select a specific population of vasovagal syncope. We believe that a comprehensive clinical history remains the best method for diagnosing vasovagal syncope. The follow-up time of one year may seem to be rather short because the long-term outcome for patients with vasovagal syncope is not well established. However, even with a longer follow-up period for our patients, we do not think that the results would have been different, due to the trend shown by the Kaplan-Meier curves.

The power of our study is 80%; with these initial data, the chances that our study was erroneously negative (the type II error) is 20%. However, from our data, the treatment of these patients showed a lack of efficacy of atenolol, which could even be worse than the placebo in some patients, and it would be unethical to continue the study. It has been estimated that, even with a greater number of patients, it would have been impossible to show any significant difference between atenolol and placebo.

Conclusions. The main result of this study is that the recurrence of vasovagal syncope in highly symptomatic

patients treated with atenolol is similar to that of those treated with a placebo. The result of the head-up tilt test was not useful in predicting the response to the drug. This study reinforces the necessity for randomized, prospective and placebo-controlled trials to evaluate the benefit of any therapy for patients with neurocardiogenic syncope.

Acknowledgments

The authors thank Dr. Victor Abraira, from the Biomedical Statistic Unit, and Angeles Mejía, a nurse from the Arrhythmia Unit, Ramón y Cajal Hospital, for their assistance.

Reprint requests and correspondence: Concepción Moro, Unidad de Arritmias, Hospital Ramón y Cajal, Carretera Colmenar Viejo Km. 9,100, 28034 Madrid, Spain. E-mail: cmoro@hrc.insalud.es.

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